

Revised in November 2021 according to MoHs guidelines.

1. NAME OF THE MEDICINAL PRODUCT

Vectibix 20 mg/mL concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of concentrate contains 20 mg panitumumab.

Each vial contains either 100 mg of panitumumab in 5 mL, or 400 mg of panitumumab in 20 mL.

When prepared according to the instructions given in section 6.6, the final panitumumab concentration should not exceed 10 mg/mL.

Panitumumab is a fully human monoclonal IgG2 antibody produced in a mammalian cell line (CHO) by recombinant DNA technology.

Excipient with known effect

Each mL of concentrate contains 0.150 mmol sodium, which is 3.45 mg sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

Colorless, pH 5.6 to 6.0 solution that may contain translucent-to-white, visible amorphous, proteinaceous panitumumab particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

In combination with chemotherapy for the treatment of unresectable, advanced or recurrent colorectal cancer (mCRC) with wild-type RAS.

Monotherapy for the treatment of patients with metastatic colorectal carcinoma with wild-type RAS after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens.

4.2 Posology and method of administration

Vectibix treatment should be supervised by a physician experienced in the use of anti-cancer therapy. Evidence of wild-type *RAS* (*KRAS* and *NRAS*) status is required before initiating treatment with Vectibix. Mutational status should be determined by an experienced laboratory using validated test methods for detection of *KRAS* (exons 2, 3, and 4) and *NRAS* (exons 2, 3, and 4) mutations.

Posology

The recommended dose of Vectibix is 6 mg/kg of body weight given once every two weeks.

Modification of the dose of Vectibix may be necessary in cases of severe (\geq grade 3) dermatological reactions as follows:

Occurrence of skin symptom(s): \geq grade 3 ¹	Administration of Vectibix	Outcome	Dose regulation
Initial occurrence	Withhold 1 or 2 doses	Improved (< grade 3)	Continuing infusion at 100% of original dose
		Not recovered	Discontinue
At the second occurrence	Withhold 1 or 2 doses	Improved (< grade 3)	Continuing infusion at 80% of original dose
		Not recovered	Discontinue
At the third occurrence	Withhold 1 or 2 doses	Improved (< grade 3)	Continuing infusion at 60% of original dose
		Not recovered	Discontinue
At the fourth occurrence	Discontinue	-	-

¹ Greater than or equal to grade 3 is defined as severe or life-threatening

Special populations

The safety and efficacy of Vectibix have not been studied in patients with renal or hepatic impairment.

There is no clinical data to support dose adjustments in the elderly.

Pediatric population

There is no relevant use of Vectibix in the pediatric population in the indication treatment of colorectal cancer.

Method of administration

Vectibix must be administered as an intravenous infusion via an infusion pump.

Prior to infusion, Vectibix should be diluted in sodium chloride 9 mg/mL (0.9%) solution for injection to a final concentration not to exceed 10 mg/mL (for preparation instructions, see section 6.6).

Vectibix must be administered using a low protein binding 0.2 or 0.22 micrometer in-line filter, through a peripheral line or indwelling catheter. The recommended infusion time is approximately 60 minutes. If the first infusion is tolerated, then subsequent infusions may be administered over 30 to 60 minutes. Doses higher than 1,000 mg should be infused over approximately 90 minutes (for handling instructions, see section 6.6).

The infusion line should be flushed with sodium chloride solution before and after Vectibix administration to avoid mixing with other medicinal products or intravenous solutions.

A reduction in the rate of infusion of Vectibix may be necessary in cases of infusion-related reactions (see section 4.4).

Vectibix must not be administered as an intravenous push or bolus.

For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Patients with a history of severe or life-threatening hypersensitivity to the active substance or to any of the excipients listed in section 6.1 (see section 4.4).

Patients with interstitial pneumonitis or pulmonary fibrosis (see section 4.4).

The combination of Vectibix with oxaliplatin-containing chemotherapy is contraindicated for patients with mutant *RAS* mCRC or for whom *RAS* mCRC status is unknown (see section 4.4).

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Dermatologic reactions and soft tissue toxicity

Dermatologic related reactions, a pharmacologic effect observed with epidermal growth factor receptor (EGFR) inhibitors, are experienced with nearly all patients (approximately 94%) treated with Vectibix. Severe (NCI-CTC grade 3) skin reactions were reported in 23% and life-threatening (NCI-CTC grade 4) skin reactions in < 1% of patients who received Vectibix monotherapy and in combination with chemotherapy (n = 2,224) (see section 4.8). If a patient develops dermatologic reactions that are grade 3 (CTCAE v 4.0) or higher, or that are considered intolerable, see the recommendation for dose modification in section 4.2.

In clinical studies, subsequent to the development of severe dermatologic reactions (including stomatitis), infectious complications including sepsis and necrotizing fasciitis, in rare cases leading to death, and local abscesses requiring incisions and drainage were reported. Patients who have severe dermatologic reactions or soft tissue toxicity or who develop worsening reactions whilst receiving Vectibix should be monitored for the development of inflammatory or infectious sequelae (including cellulitis and necrotizing fasciitis), and appropriate treatment promptly initiated. Life-threatening and fatal infectious complications including necrotizing fasciitis and sepsis have been observed in patients treated with Vectibix. Rare cases of Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported in patients treated with Vectibix in the post-marketing setting. Withhold or discontinue Vectibix in the event of dermatologic or soft tissue toxicity associated with severe or life-threatening inflammatory or infectious complications.

Treatment and management of dermatologic reactions should be based on severity and may include a moisturizer, sunscreen (SPF > 15 UVA and UVB), and topical steroid cream (not stronger than 1% hydrocortisone) applied to affected areas, and/or oral antibiotics (e.g. doxycycline). It is also recommended that patients experiencing rash/dermatological toxicities wear sunscreen and hats and limit sun exposure as sunlight can exacerbate any skin reactions that may occur. Patients may be advised to apply moisturizer and sunscreen to face, hands, feet, neck, back and chest every morning during treatment, and to apply the topical steroid to face, hands, feet, neck, back and chest every night during treatment.

Pulmonary complications

Patients with a history of, or evidence of, interstitial pneumonitis or pulmonary fibrosis were excluded from clinical studies. Cases of Interstitial Lung Disease (ILD), both fatal and non-fatal, have been reported, mainly from the Japanese population. In the event of acute onset or worsening pulmonary symptoms, Vectibix treatment should be interrupted and a prompt investigation of these symptoms should occur. If ILD is diagnosed, Vectibix should be permanently discontinued and the patient should be treated appropriately. In patients with a history of interstitial pneumonitis or pulmonary fibrosis, the benefits of therapy with panitumumab versus the risk of pulmonary complications must be carefully considered.

Electrolyte disturbances

Progressively decreasing serum magnesium levels leading to severe (grade 4) hypomagnesemia have been observed in some patients. Patients should be periodically monitored for hypomagnesemia and accompanying hypocalcemia prior to initiating Vectibix treatment, and periodically thereafter for up to 8 weeks after the completion of treatment (see section 4.8). Magnesium repletion is recommended, as appropriate.

Other electrolyte disturbances, including hypokalemia, have also been observed. Monitoring as above and repletion as appropriate of these electrolytes is also recommended.

Infusion-related reactions

Across monotherapy and combination mCRC clinical studies (n = 2,224), infusion-related reactions (occurring within 24 hours of an infusion) were reported in Vectibix-treated patients, including severe infusion-related reactions (NCI-CTC grade 3 and grade 4).

In the post-marketing setting, serious infusion-related reactions have been reported, including rare post-marketing reports with a fatal outcome. If a severe or life-threatening reaction occurs during an infusion or at any time post-infusion [e.g. presence of bronchospasm, angioedema, hypotension, need for parenteral treatment, or anaphylaxis], Vectibix should be permanently discontinued (see sections 4.3 and 4.8).

In patients experiencing a mild or moderate (CTCAE v 4.0 grades 1 and 2) infusion-related reaction the infusion rate should be reduced for the duration of that infusion. It is recommended to maintain this lower infusion rate in all subsequent infusions.

Hypersensitivity reactions occurring more than 24 hours after infusion have been reported including a fatal case of angioedema that occurred more than 24 hours after the infusion. Patients should be informed of the possibility of a late onset reaction and instructed to contact their physician if symptoms of a hypersensitivity reaction occur.

Acute renal failure

Acute renal failure has been observed in patients who develop severe diarrhea and dehydration. Patients who experience severe diarrhea should be instructed to consult a healthcare professional urgently.

Vectibix in combination with irinotecan, bolus 5-fluorouracil, and leucovorin (IFL) chemotherapy

Patients receiving Vectibix in combination with the IFL regimen [bolus 5-fluorouracil (500 mg/m²), leucovorin (20 mg/m²) and irinotecan (125 mg/m²)] experienced a high incidence of severe diarrhea (see section 4.8). Therefore, administration of Vectibix in combination with IFL should be avoided (see section 4.5).

Vectibix in combination with bevacizumab and chemotherapy regimens

Shortened progression-free survival time and increased deaths were observed in the patients receiving Vectibix in combination with bevacizumab and chemotherapy. A greater frequency of pulmonary embolism, infections (predominantly of dermatologic origin), diarrhea, electrolyte imbalances, nausea, vomiting and dehydration was also observed in the treatment arms using Vectibix in combination with bevacizumab and chemotherapy. Vectibix should not be administered in combination with bevacizumab-containing chemotherapy (see sections 4.5 and 5.1).

Vectibix in combination with oxaliplatin-based chemotherapy in patients with mutant *RAS* mCRC or for whom *RAS* tumor status is unknown

The combination of Vectibix with oxaliplatin-containing chemotherapy is contraindicated for patients with mutant *RAS* mCRC or for whom *RAS* mCRC status is unknown (see sections 4.3 and 5.1).

A shortened progression-free survival (PFS) and overall survival (OS) time were observed in patients with mutant *KRAS* (exon 2) tumors and additional *RAS* mutations (*KRAS* [exons 3 and 4] or *NRAS* [exons 2, 3, 4]) who received panitumumab in combination with infusional 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX) versus FOLFOX alone (see section 5.1).

RAS mutational status should be determined using a validated test method by an experienced laboratory (see section 4.2). If Vectibix is to be used in combination with FOLFOX then it is recommended that mutational status be determined by a laboratory that participates in a *RAS* External Quality Assurance program or wild-type status be confirmed in a duplicate test.

Ocular toxicities

Serious cases of keratitis and ulcerative keratitis, which may lead to corneal perforation, have been reported. Patients presenting with signs and symptoms suggestive of keratitis such as acute or worsening: eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye should be referred promptly to an ophthalmology specialist.

If a diagnosis of ulcerative keratitis is confirmed, treatment with Vectibix should be interrupted or discontinued. If keratitis is diagnosed, the benefits and risks of continuing treatment should be carefully considered.

Vectibix should be used with caution in patients with a history of keratitis, ulcerative keratitis or severe dry eye. Contact lens use is also a risk factor for keratitis and ulceration.

Patients with ECOG 2 performance status treated with Vectibix in combination with chemotherapy

For patients with ECOG 2 performance status, assessment of benefit-risk is recommended prior to initiation of Vectibix in combination with chemotherapy for treatment of mCRC. A positive benefit-risk balance has not been documented in patients with ECOG 2 performance status.

Elderly patients

No overall differences in safety or efficacy were observed in elderly patients (≥ 65 years of age) treated with Vectibix monotherapy. However, an increased number of serious adverse reactions were reported in elderly patients treated with Vectibix in combination with FOLFIRI or FOLFOX chemotherapy compared to chemotherapy alone (see section 4.8).

Warnings for excipients

This medicinal product contains 3.45 mg sodium per mL, equivalent to 0.17% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Data from an interaction study involving Vectibix and irinotecan in patients with mCRC indicated that the pharmacokinetics of irinotecan and its active metabolite, SN-38, are not altered when the medicinal products are co-administered. Results from a cross-study comparison indicated that irinotecan-containing regimens (IFL or FOLFIRI) have no effect on the pharmacokinetics of panitumumab.

Vectibix should not be administered in combination with IFL chemotherapy or with bevacizumab-containing chemotherapy. A high incidence of severe diarrhea was observed when panitumumab was administered in combination with IFL (see section 4.4), and increased toxicity and deaths were seen when panitumumab was combined with bevacizumab and chemotherapy (see sections 4.4 and 5.1).

The combination of Vectibix with oxaliplatin-containing chemotherapy is contraindicated for patients with mutant *RAS* mCRC or for whom *RAS* mCRC status is unknown. A shortened progression-free survival and overall survival time were observed in a clinical study in patients with mutant *RAS* tumors who received panitumumab and FOLFOX (see sections 4.4 and 5.1).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of Vectibix in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. EGFR has been implicated in the control of pre-natal development and may be essential for normal organogenesis, proliferation, and differentiation in the developing embryo. Therefore, Vectibix has the potential to cause fetal harm when administered to pregnant women.

Human IgG is known to cross the placental barrier, and panitumumab may therefore be transmitted from the mother to the developing fetus. In women of childbearing potential, appropriate contraceptive measures must be used during treatment with Vectibix, and for 2 months following the last dose. If Vectibix is used during pregnancy or if the patient becomes pregnant while receiving this medicinal product, she should be advised of the potential risk for loss of the pregnancy or potential hazard to the fetus.

Breast-feeding

It is unknown whether panitumumab is excreted in human breast milk. Because human IgG is secreted into human milk, panitumumab might also be secreted. The potential for absorption and harm to the infant after ingestion is unknown. It is recommended that women do not breast-feed during treatment with Vectibix and for 2 months after the last dose.

Fertility

Animal studies have shown reversible effects on the menstrual cycle and reduced female fertility in monkeys (see section 5.3). Panitumumab may impact the ability of a woman to become pregnant.

4.7 Effects on ability to drive and use machines

Vectibix may have a minor influence on the ability to drive and use machines. If patients experience treatment-related symptoms affecting their vision and/or ability to concentrate and react, it is recommended that they do not drive or use machines until the effect subsides.

4.8 Undesirable effects

Summary of safety profile

Based on an analysis of all mCRC clinical trial patients receiving Vectibix monotherapy and in combination with chemotherapy (n = 2,224), the most commonly reported adverse reactions are skin reactions occurring in approximately 94% of patients. These reactions are related to the pharmacologic effects of Vectibix, and the majority are mild to moderate in nature with 23% severe (grade 3 NCI-CTC) and < 1% life-threatening (grade 4 NCI-CTC). For clinical management of skin reactions, including dose modification recommendations, see section 4.4.

Very commonly reported adverse reactions occurring in $\geq 20\%$ of patients were gastrointestinal disorders [diarrhea (46%), nausea (39%), vomiting (26%), constipation (23%) and abdominal pain (23%)]; general disorders [fatigue (35%), pyrexia (21%)]; metabolism and nutrition disorders [decreased appetite (30%)]; infections and infestations [paronychia (20%)]; and skin and subcutaneous disorders [rash (47%), dermatitis acneiform (39%), pruritus (36%), erythema (33%) and dry skin (21%)].

Tabulated list of adverse reactions

The data in the table below describe adverse reactions reported from clinical studies in patients with mCRC who received panitumumab as a single agent or in combination with chemotherapy (n = 2,224) and spontaneous reporting. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

	Adverse reactions		
MedDRA system organ class	Very common ($\geq 1/10$)	Common ($\geq 1/100$ to $< 1/10$)	Uncommon ($\geq 1/1,000$ to $< 1/100$)
Infections and infestations	Conjunctivitis Paronychia ¹	Rash pustular Cellulitis ¹ Urinary tract infection Folliculitis Localized infection	Eye infection Eyelid infection
Blood and lymphatic system disorders	Anemia	Leukopenia	
Immune system disorders		Hypersensitivity ¹	Anaphylactic reaction ²
Metabolism and nutrition disorders	Hypokalemia Hypomagnesemia Decreased appetite	Hypocalcemia Dehydration Hyperglycemia Hypophosphatemia	
Psychiatric disorders	Insomnia	Anxiety	
Nervous system disorders		Headache Dizziness	
Eye disorders		Blepharitis Growth of eyelashes Lacrimation increased Ocular hyperemia Dry eye Eye pruritus Eye irritation	Ulcerative keratitis ^{1,4} Keratitis ¹ Eyelid irritation
Cardiac disorders		Tachycardia	Cyanosis
Vascular disorders		Deep vein thrombosis Hypotension Hypertension Flushing	
Respiratory, thoracic and mediastinal disorders	Dyspnea Cough	Pulmonary embolism Epistaxis	Interstitial lung disease ³ Bronchospasm Nasal dryness
Gastrointestinal disorders	Diarrhea ¹ Nausea Vomiting Abdominal pain Stomatitis Constipation	Rectal hemorrhage Dry mouth Dyspepsia Aphthous ulcer Cheilitis Gastroesophageal reflux disease	Chapped lips Dry lips

MedDRA system organ class	Adverse reactions		
	Very common (≥ 1/10)	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)
Skin and subcutaneous tissue disorders ¹	Dermatitis acneiform Rash Erythema Pruritus Dry skin Skin fissures Acne Alopecia	Skin ulcer Skin exfoliation Exfoliative rash Dermatitis Rash papular Rash pruritic Rash erythematous Rash generalized Rash macular Rash maculo-papular Skin lesion Skin toxicity Scab Hypertrichosis Onychoclasia Nail disorder Hyperhidrosis Palmar-plantar erythrodysesthesia syndrome	Toxic epidermal necrolysis ^{1,4} Stevens-Johnson syndrome ^{1,4} Skin necrosis ^{1,4} Angioedema ¹ Hirsutism Ingrowing nail Onycholysis
Musculoskeletal and connective tissue disorders	Back pain	Pain in extremity	
General disorders and administration site conditions	Fatigue Pyrexia Asthenia Mucosal inflammation Edema peripheral	Chest pain Pain Chills	
Injury, poisoning and procedural complications			Infusion-related reaction ¹
Investigations	Weight decreased	Blood magnesium decreased	

¹ See section “Description of selected adverse reactions” below

² See section 4.4 Infusion-related reactions

³ See section 4.4 Pulmonary complications

⁴ Skin necrosis, Stevens-Johnson syndrome, toxic epidermal necrolysis and ulcerative keratitis are panitumumab ADRs that were reported in the post-marketing setting. For these ADRs the maximum frequency category was estimated from the upper limit of 95% confidence interval for the point estimate based on regulatory guidelines for estimation of the frequency of adverse reactions from spontaneous reporting. The maximum frequency estimated from the upper limit of 95% confidence interval for the point estimate, i.e., 3/2,224 (or 0.13%).

The safety profile of Vectibix in combination with chemotherapy consisted of the reported adverse reactions of Vectibix (as a monotherapy) and the toxicities of the background chemotherapy regimen. No new toxicities or worsening of previously recognized toxicities beyond the expected additive effects were observed. Skin reactions were the most frequently occurring adverse reactions in patients receiving panitumumab in combination with chemotherapy. Other toxicities that were observed with a greater frequency relative to monotherapy included hypomagnesemia, diarrhea, and stomatitis. These toxicities infrequently led to discontinuation of Vectibix or of chemotherapy.

Description of selected adverse reactions

Gastrointestinal disorders

Diarrhea when reported was mainly mild or moderate in severity. Severe diarrhea (NCI-CTC grade 3 and 4) was reported in 2% of patients treated with Vectibix as a monotherapy and in 16% of patients treated with Vectibix in combination with chemotherapy.

There have been reports of acute renal failure in patients who develop diarrhea and dehydration (see section 4.4).

Infusion-related reactions

Across monotherapy and combination mCRC clinical studies (n = 2,224), infusion-related reactions (occurring within 24 hours of any infusion), which may include symptoms/signs such as chills, fever or dyspnea, were reported in approximately 5% of Vectibix-treated patients, of which 1% were severe (NCI-CTC grade 3 and grade 4).

A case of fatal angioedema occurred in a patient with recurrent and metastatic squamous cell carcinoma of the head and neck treated with Vectibix in a clinical trial. The fatal event occurred after re-exposure following a prior episode of angioedema; both episodes occurred greater than 24 hours after administration (see sections 4.3 and 4.4). Hypersensitivity reactions occurring more than 24 hours after infusion have also been reported in the post-marketing setting.

For clinical management of infusion-related reactions, see section 4.4.

Skin and subcutaneous tissue disorders

Skin rash most commonly occurred on the face, upper chest, and back, but could extend to the extremities. Subsequent to the development of severe skin and subcutaneous reactions, infectious complications including sepsis, in rare cases leading to death, cellulitis and local abscesses requiring incisions and drainage were reported. The median time to first symptom of dermatologic reaction was 10 days, and the median time to resolution after the last dose of Vectibix was 31 days.

Paronychia inflammation was associated with swelling of the lateral nail folds of the toes and fingers.

Dermatological reactions (including nail effects), observed in patients treated with Vectibix or other EGFR inhibitors, are known to be associated with the pharmacologic effects of therapy.

Across all clinical trials, skin reactions occurred in approximately 94% of patients receiving Vectibix as monotherapy or in combination with chemotherapy (n = 2,224). These events consisted predominantly of rash and dermatitis acneiform and were mostly mild to moderate in severity. Severe (NCI-CTC grade 3) skin reactions were reported in 23% and life-threatening (NCI-CTC grade 4) skin reactions in < 1% of patients. Life-threatening and fatal infectious complications including necrotizing fasciitis and sepsis have been observed in patients treated with Vectibix (see section 4.4).

For clinical management of dermatological reactions, including dose modification recommendations, see section 4.4.

In the post-marketing setting, rare cases of skin necrosis, Stevens-Johnson syndrome and toxic epidermal necrolysis (see section 4.4) have been reported.

Ocular toxicities

Serious cases of keratitis and ulcerative keratitis, which may lead to corneal perforation, have been reported (see section 4.4).

Other special populations

No overall differences in safety or efficacy were observed in elderly patients (≥ 65 years of age) treated with Vectibix monotherapy. However, an increased number of serious adverse events were reported in elderly patients treated with Vectibix in combination with FOLFIRI (45% versus 32%) or FOLFOX (52% versus 37%) chemotherapy compared to chemotherapy alone (see section 4.4). The most increased serious adverse events included diarrhea in patients treated with Vectibix in

combination with either FOLFOX or FOLFIRI, and dehydration and pulmonary embolism when patients were treated with Vectibix in combination with FOLFIRI.

The safety of Vectibix has not been studied in patients with renal or hepatic impairment.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

<https://sideeffects.health.gov.il/>

4.9 Overdose

Doses up to 9 mg/kg have been tested in clinical trials. There have been reports of overdose at doses up to approximately twice the recommended therapeutic dose (12 mg/kg). Adverse events observed included skin toxicity, diarrhea, dehydration and fatigue and were consistent with the safety profile at the recommended dose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies, ATC code: L01XC08

Mechanism of action

Panitumumab is a recombinant, fully human IgG2 monoclonal antibody that binds with high-affinity and specificity to the human EGFR. EGFR is a transmembrane glycoprotein that is a member of a subfamily of type I receptor tyrosine kinases including EGFR (HER1/c-ErbB-1), HER2, HER3, and HER4. EGFR promotes cell growth in normal epithelial tissues, including the skin and hair follicle, and is expressed on a variety of tumor cells.

Panitumumab binds to the ligand binding domain of EGFR and inhibits receptor autophosphorylation induced by all known EGFR ligands. Binding of panitumumab to EGFR results in internalization of the receptor, inhibition of cell growth, induction of apoptosis, and decreased interleukin 8 and vascular endothelial growth factor production.

KRAS (Kirsten rat sarcoma 2 viral oncogene homologue) and *NRAS* (Neuroblastoma *RAS* viral oncogene homologue) are highly related members of the *RAS* oncogene family. *KRAS* and *NRAS* genes encode small, GTP-binding proteins involved in signal transduction. A variety of stimuli, including that from the EGFR activate *KRAS* and *NRAS* which in turn stimulate other intracellular proteins to promote cell proliferation, cell survival and angiogenesis.

Activating mutations in the *RAS* genes occur frequently in a variety of human tumors and have been implicated in both oncogenesis and tumor progression.

Pharmacodynamic effects

In vitro assays and *in vivo* animal studies have shown that panitumumab inhibits the growth and survival of tumor cells expressing EGFR. No anti-tumor effects of panitumumab were observed in human tumor xenografts lacking EGFR expression. The addition of panitumumab to radiation, chemotherapy or other targeted therapeutic agents, in animal studies resulted in an increase in anti-tumor effects compared to radiation, chemotherapy or targeted therapeutic agents alone.

Dermatological reactions (including nail effects), observed in patients treated with Vectibix or other EGFR inhibitors, are known to be associated with the pharmacologic effects of therapy (with cross-reference to sections 4.2 and 4.8).

Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. Data on the development of anti-panitumumab antibodies has been evaluated using two different screening immunoassays for the detection of binding anti-panitumumab antibodies (an ELISA which detects high-affinity antibodies, and a Biosensor Immunoassay which detects both high and low-affinity antibodies). For patients whose sera tested positive in either screening immunoassay, an *in vitro* biological assay was performed to detect neutralizing antibodies.

As monotherapy:

- The incidence of binding antibodies (excluding predose and transient positive patients) was < 1% as detected by the acid-dissociation ELISA and 3.8% as detected by the Biacore assay;
- The incidence of neutralizing antibodies (excluding predose and transient positive patients) was < 1%;
- Compared with patients who did not develop antibodies, no relationship between the presence of anti-panitumumab antibodies and pharmacokinetics, efficacy and safety has been observed.

In combination with irinotecan- or oxaliplatin-based chemotherapy:

- The incidence of binding antibodies (excluding predose positive patients) was 1% as detected by the acid-dissociation ELISA and < 1% as detected by the Biacore assay;
- The incidence of neutralizing antibodies (excluding predose positive patients) was < 1%;
- No evidence of an altered safety profile was found in patients who tested positive for antibodies to Vectibix.

The detection of antibody formation is dependent on the sensitivity and specificity of the assay. The observed incidence of antibody positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medicinal products and underlying disease, therefore, comparison of the incidence of antibodies to other products may be misleading.

Clinical efficacy as monotherapy

The efficacy of Vectibix as monotherapy in patients with metastatic colorectal cancer (mCRC) who had disease progression during or after prior chemotherapy was studied in open-label, single-arm trials (585 patients) and in two randomized controlled trials versus best supportive care (463 patients) and versus cetuximab (1,010 patients).

A multinational, randomized, controlled trial was conducted in 463 patients with EGFR-expressing metastatic carcinoma of the colon or rectum after confirmed failure of oxaliplatin and irinotecan-containing regimens. Patients were randomized 1:1 to receive Vectibix at a dose of 6 mg/kg given once every two weeks plus best supportive care (not including chemotherapy) (BSC) or BSC alone. Patients were treated until disease progression or unacceptable toxicity occurred. Upon disease progression BSC alone patients were eligible to crossover to a companion study and receive Vectibix at a dose of 6 mg/kg given once every two weeks.

The primary endpoint was PFS. The study was retrospectively analyzed by wild-type *KRAS* (exon 2) status versus mutant *KRAS* (exon 2) status. Tumor samples obtained from the primary resection of colorectal cancer were analyzed for the presence of the seven most common activating mutations in the codon 12 and 13 of the *KRAS* gene. 427 (92%) patients were evaluable for *KRAS* status of which 184 had mutations. The efficacy results from an analysis adjusting for potential bias from unscheduled assessments are shown in the table below. There was no difference in overall survival (OS) seen in either group.

	Wild-type <i>KRAS</i> (exon 2) population		Mutant <i>KRAS</i> (exon 2) population	
	Vectibix plus BSC (n = 124)	BSC (n = 119)	Vectibix plus BSC (n = 84)	BSC (n = 100)
ORR n (%)	17%	0%	0%	0%
Response rate (investigator assessed) ^a (95% CI)	22% (14, 32)		0% (0, 4)	
Stable disease	34%	12%	12%	8%
PFS				
Hazard ratio (95% CI)	0.49 (0.37, 0.65), p < 0.0001		1.07 (0.77, 1.48), p = 0.6880	
Median (weeks)	16.0	8.0	8.0	8.0

CI = confidence interval

^a In patients that crossed over to panitumumab after progression on BSC alone (95% CI)

In an exploratory analysis of banked tumor specimens from this study, 11 of 72 patients (15%) with wild-type *RAS* tumors receiving panitumumab had an objective response compared to only 1 of 95 patients (1%) with mutant *RAS* tumor status. Moreover, panitumumab treatment was associated with improved PFS compared to BSC in patients with wild-type *RAS* tumors (HR = 0.38 [95% CI: 0.27, 0.56]), but not in patients with tumors harboring a *RAS* mutation (HR = 0.98 [95% CI: 0.73, 1.31]).

The efficacy of Vectibix was also evaluated in an open-label trial in patients with wild-type *KRAS* (exon 2) mCRC. A total of 1,010 patients refractory to chemotherapy were randomized 1:1 to receive Vectibix or cetuximab to test whether Vectibix is non-inferior to cetuximab. The primary endpoint was OS. Secondary endpoints included PFS and objective response rate (ORR).

The efficacy results for the study are presented in the table below.

Wild-type <i>KRAS</i> (exon 2) population	Vectibix (n = 499)	Cetuximab (n = 500)
OS		
Median (months) (95% CI)	10.4 (9.4, 11.6)	10.0 (9.3, 11.0)
Hazard ratio (95% CI)	0.97 (0.84, 1.11)	
PFS		
Median (months) (95% CI)	4.1 (3.2, 4.8)	4.4 (3.2, 4.8)
Hazard ratio (95% CI)	1.00 (0.88, 1.14)	
ORR		
n (%) (95% CI)	22% (18%, 26%)	20% (16%, 24%)
Odds ratio (95% CI)	1.15 (0.83, 1.58)	

Overall, the safety profile of panitumumab was similar to that of cetuximab, in particular regarding skin toxicity. However, infusion reactions were more frequent with cetuximab (13% versus 3%) but electrolyte disturbances were more frequent with panitumumab, especially hypomagnesemia (29% versus 19%).

Clinical efficacy in combination with chemotherapy

Among patients with wild-type *RAS* mCRC, PFS, OS, and ORR were improved for subjects receiving panitumumab plus chemotherapy (FOLFOX or FOLFIRI) compared with those receiving chemotherapy alone. Patients with additional *RAS* mutations beyond *KRAS* exon 2 were unlikely to benefit from the addition of panitumumab to FOLFIRI and a detrimental effect was seen with the addition of panitumumab to FOLFOX in these patients. *BRAF* mutations in exon 15 were found to be prognostic of worse outcome. *BRAF* mutations were not predictive of the outcome for panitumumab treatment in combination with FOLFOX or FOLFIRI.

First-line combination with FOLFOX

The efficacy of Vectibix in combination with oxaliplatin, 5-fluorouracil (5-FU), and leucovorin (FOLFOX) was evaluated in a randomized, controlled trial of 1,183 patients with mCRC with the primary endpoint of PFS. Other key endpoints included the OS, ORR, time to response, time to progression (TTP), and duration of response. The study was prospectively analyzed by tumor *KRAS* (exon 2) status which was evaluable in 93% of the patients.

A predefined retrospective subset analysis of 641 patients of the 656 patients with wild-type *KRAS* (exon 2) mCRC was performed. Patient tumor samples with wild-type *KRAS* exon 2 (codons 12/13) status were tested for additional *RAS* mutations in *KRAS* exon 3 (codons 61) and exon 4 (codons 117/146) and *NRAS* exon 2 (codons 12/13), exon 3 (codon 61), and exon 4 (codons 117/146) and *BRAF* exon 15 (codon 600). The incidence of these additional *RAS* mutations in the wild-type *KRAS* exon 2 population was approximately 16%.

Results in patients with wild-type *RAS* mCRC and mutant *RAS* mCRC are presented in the table below.

	Vectibix plus FOLFOX (months) Median (95% CI)	FOLFOX (months) Median (95% CI)	Difference (months)	Hazard ratio (95% CI)
Wild-type <i>RAS</i> population				
PFS	10.1 (9.3, 12.0)	7.9 (7.2, 9.3)	2.2	0.72 (0.58, 0.90)
OS	26.0 (21.7, 30.4)	20.2 (17.7, 23.1)	5.8	0.78 (0.62, 0.99)
Mutant <i>RAS</i> population				
PFS	7.3 (6.3, 7.9)	8.7 (7.6, 9.4)	-1.4	1.31 (1.07, 1.60)
OS	15.6 (13.4, 17.9)	19.2 (16.7, 21.8)	-3.6	1.25 (1.02, 1.55)

Additional mutations in *KRAS* and *NRAS* at exon 3 (codon 59) were subsequently identified (n = 7). An exploratory analysis showed similar results to those in the previous table.

Combination with FOLFIRI

The efficacy of Vectibix in second-line in combination with irinotecan, 5-fluorouracil (5-FU) and leucovorin (FOLFIRI) was evaluated in a randomized, controlled trial of 1,186 patients with mCRC with the primary endpoints of OS and PFS. Other key endpoints included the ORR, time to response, TTP, and duration of response. The study was prospectively analyzed by tumor *KRAS* (exon 2) status which was evaluable in 91% of the patients.

A predefined retrospective subset analysis of 586 patients of the 597 patients with wild-type *KRAS* (exon 2) mCRC was performed, where tumor samples from these patients were tested for additional *RAS* and *BRAF* mutations as previously described. The *RAS/BRAF* ascertainment was 85% (1,014 of 1,186 randomized patients). The incidence of these additional *RAS* mutations (*KRAS* exons 3, 4 and *NRAS* exons 2, 3, 4) in the wild-type *KRAS* (exon 2) population was approximately 19%. The incidence of *BRAF* exon 15 mutation in the wild-type *KRAS* (exon 2) population was approximately 8%. Efficacy results in patients with wild-type *RAS* mCRC and mutant *RAS* mCRC are shown in the below table.

	Vectibix plus FOLFIRI (months) Median (95% CI)	FOLFIRI (months) Median (95% CI)	Hazard ratio (95% CI)
Wild-type RAS population			
PFS	6.4 (5.5, 7.4)	4.6 (3.7, 5.6)	0.70 (0.54, 0.91)
OS	16.2 (14.5, 19.7)	13.9 (11.9, 16.0)	0.81 (0.63, 1.02)
Mutant RAS population			
PFS	4.8 (3.7, 5.5)	4.0 (3.6, 5.5)	0.86 (0.70, 1.05)
OS	11.8 (10.4, 13.1)	11.1 (10.2, 12.4)	0.91 (0.76, 1.10)

The efficacy of Vectibix in first-line in combination with FOLFIRI was evaluated in a single-arm study of 154 patients with the primary endpoint of objective response rate (ORR). Other key endpoints included the PFS, time to response, TTP, and duration of response.

A predefined retrospective subset analysis of 143 patients of the 154 patients with wild-type *KRAS* (exon 2) mCRC was performed, where tumor samples from these patients were tested for additional *RAS* mutations. The incidence of these additional *RAS* mutations (*KRAS* exons 3, 4 and *NRAS* exons 2, 3, 4) in the wild-type *KRAS* (exon 2) population was approximately 10%.

Results in patients with wild-type *RAS* mCRC and mutant *RAS* mCRC from the primary analysis are presented in the table below.

	Panitumumab + FOLFIRI	
	Wild-type RAS (n = 69)	Mutant RAS (n = 74)
ORR (%) (95% CI)	59 (46, 71)	41 (30, 53)
Median PFS (months) (95% CI)	11.2 (7.6, 14.8)	7.3 (5.8, 7.5)
Median duration of response (months) (95% CI)	13.0 (9.3, 15.7)	5.8 (3.9, 7.8)
Median TTP (months) (95% CI)	13.2 (7.8, 17.0)	7.3 (6.1, 7.6)

First-line combination with bevacizumab and oxaliplatin or irinotecan-based chemotherapy

In a randomized, open-label, controlled clinical trial, chemotherapy (oxaliplatin or irinotecan) and bevacizumab were given with and without panitumumab in the first-line treatment of patients with metastatic colorectal cancer (n = 1,053 [n = 823 oxaliplatin cohort, n = 230 irinotecan cohort]). Panitumumab treatment was discontinued due to a statistically significant reduction in PFS in patients receiving panitumumab observed in an interim analysis.

The major study objective was comparison of PFS in the oxaliplatin cohort. In the final analysis, the hazard ratio for PFS was 1.27 (95% CI: 1.06, 1.52). Median PFS was 10.0 (95% CI: 8.9, 11.0) and 11.4 (95% CI: 10.5, 11.9) months in the panitumumab and the non-panitumumab arm, respectively. There was an increase in mortality in the panitumumab arm. The hazard ratio for overall survival was 1.43 (95% CI: 1.11, 1.83). Median overall survival was 19.4 (95% CI: 18.4, 20.8) and 24.5 (95% CI: 20.4, 24.5) in the panitumumab arm and the non-panitumumab arm.

An additional analysis of efficacy data by *KRAS* (exon 2) status did not identify a subset of patients who benefited from panitumumab in combination with oxaliplatin- or irinotecan-based chemotherapy and bevacizumab. For the wild-type *KRAS* subset of the oxaliplatin cohort, the hazard ratio for PFS

was 1.36 with 95% CI: 1.04-1.77. For the mutant *KRAS* subset, the hazard ratio for PFS was 1.25 with 95% CI: 0.91-1.71. A trend for OS favouring the control arm was observed in the wild-type *KRAS* subset of the oxaliplatin cohort (hazard ratio = 1.89; 95% CI: 1.30, 2.75). A trend towards worse survival was also observed with panitumumab in the irinotecan cohort regardless of *KRAS* mutational status. Overall, panitumumab treatment combined with chemotherapy and bevacizumab is associated with an unfavourable benefit-to-risk profile irrespective of tumor *KRAS* mutational status.

Pediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Vectibix in all subsets of the pediatric population in colorectal cancer (see section 4.2 for information on pediatric use).

5.2 Pharmacokinetic properties

Vectibix administered as a single agent or in combination with chemotherapy exhibits nonlinear pharmacokinetics.

Following a single-dose administration of panitumumab as a 1-hour infusion, the area under the concentration-time curve (AUC) increased in a greater than dose-proportional manner and clearance (CL) of panitumumab decreased from 30.6 to 4.6 mL/day/kg as the dose increased from 0.75 to 9 mg/kg. However, at doses above 2 mg/kg, the AUC of panitumumab increases in an approximately dose-proportional manner.

Following the recommended dose regimen (6 mg/kg given once every 2 weeks as a 1-hour infusion), panitumumab concentrations reached steady-state levels by the third infusion with mean (\pm Standard Deviation [SD]) peak and trough concentrations of 213 ± 59 and 39 ± 14 mcg/mL, respectively. The mean (\pm SD) $AUC_{0-\tau}$ and CL were $1,306 \pm 374$ mcg•day/mL and 4.9 ± 1.4 mL/kg/day, respectively. The elimination half-life was approximately 7.5 days (range: 3.6 to 10.9 days).

A population pharmacokinetic analysis was performed to explore the potential effects of selected covariates on panitumumab pharmacokinetics. Results suggest that age (21-88), gender, race, hepatic function, renal function, chemotherapeutic agents, and EGFR membrane staining intensity (1+, 2+, 3+) in tumor cells had no apparent impact on the pharmacokinetics of panitumumab.

No clinical studies have been conducted to examine the pharmacokinetics of panitumumab in patients with renal or hepatic impairment.

5.3 Preclinical safety data

Adverse reactions seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows:

Skin rash and diarrhea were the major findings observed in repeat-dose toxicity studies of up to 26 weeks duration in cynomolgus monkeys. These findings were observed at doses approximately equivalent to the recommended human dose and were reversible upon termination of administration of panitumumab. The skin rash and diarrhea observed in monkeys are considered related to the pharmacological action of panitumumab and are consistent with the toxicities observed with other anti-EGFR inhibitors.

Studies to evaluate the mutagenic and carcinogenic potential of panitumumab have not been performed.

Animal studies are insufficient with respect to embryo-fetal development since fetal panitumumab exposure levels were not examined. Panitumumab has been shown to cause fetal abortions and/or fetal deaths in cynomolgus monkeys when administered during the period of organogenesis at doses approximately equivalent to the recommended human dose.

Formal male fertility studies have not been conducted; however, microscopic evaluation of male reproductive organs from repeat-dose toxicity studies in cynomolgus monkeys at doses up to approximately 5-fold the human dose on a mg/kg basis, revealed no differences compared to control male monkeys. Fertility studies conducted in female cynomolgus monkeys showed that panitumumab may produce prolonged menstrual cycle and/or amenorrhea and reduced pregnancy rate which occurred at all doses evaluated.

No pre- and post-natal development animal studies have been conducted with panitumumab. All patients should be advised regarding the potential risk of panitumumab on pre- and post-natal development prior to initiation of Vectibix therapy.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Sodium acetate trihydrate
Acetic acid, glacial (for pH-adjustment)
Water for injections.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Vial

The expiry date of the product is indicated on the packaging materials.

Diluted solution

Vectibix does not contain any antimicrobial preservative or bacteriostatic agent. The product should be used immediately after dilution. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should be no longer than 24 hours at 2°C – 8°C. The diluted solution must not be frozen.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Do not freeze.
Store in the original carton in order to protect from light.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Type I glass vial with an elastomeric stopper, aluminum seal and flip-off plastic cap.
One vial contains either 100 mg of panitumumab in 5 mL, or 400 mg panitumumab in 20 mL of concentrate for solution for infusion.

Pack of 1 vial.

6.6 Special precautions for disposal and other handling

Vectibix is intended for single-use only. Vectibix should be diluted in sodium chloride 9 mg/mL (0.9%) solution for injection by healthcare professional using aseptic technique. Do not shake or vigorously agitate the vial. Vectibix should be inspected visually prior to administration. The solution should be colorless and may contain visible translucent-to-white, amorphous, proteinaceous particulates (which will be removed by in-line filtration). Do not administer Vectibix if its appearance is not as described above. Using only a 21-gauge or smaller diameter hypodermic needle, withdraw the necessary amount of Vectibix for a dose of 6 mg/kg. Do not use needle-free devices (e.g. vial adapters) to withdraw vial contents. Dilute in a total volume of 100 mL. The final concentration should not exceed 10 mg/mL. Doses higher than 1,000 mg should be diluted in 150 mL sodium chloride 9 mg/mL (0.9%) solution for injection (see section 4.2). The diluted solution should be mixed by gentle inversion, do not shake.

Vectibix must be administered using a low protein binding 0.2 or 0.22 micrometer in-line filter, through a peripheral line or indwelling catheter.

No incompatibilities have been observed between Vectibix and sodium chloride 9 mg/mL (0.9%) solution for injection in polyvinyl chloride bags or polyolefin bags.

Discard the vial and any liquid remaining in the vial after the single-use.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER

Amgen Europe B.V.
Minervum 7061
NL-4817 ZK Breda
The Netherlands

8. LICENSE HOLDER

Amgen Europe B.V.
P.O. BOX 53313
Tel - Aviv
Israel